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| 10/621,966 | 07/17/2003 | David Solow-Cordero | 061030-0023-US | 2041 |

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| EXAMINER | |
|---|---|
| GEMBEH, SHIRLEY V | |
| **ART UNIT** | **PAPER NUMBER** |
| 1614 | |

DATE MAILED: 01/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/621,966 | SOLOW-CORDERO ET AL. | |
| | Examiner | Art Unit | |
| | Shirley V. Gembeh | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-12,14-17,20-28 and 33-37* is/are pending in the application.

4a) Of the above claim(s) *13,18,19 and 29-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-17,20-28 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### Status of claims

Claims 1-12, 14-17, 20-28 and 33-37 and 42 are pending.

Claims 13, 18-19, 29-32, and 38-50 are withdrawn from further consideration.

Claims 24 is withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a non-elected invention or subject matter modulators are not Formula I.

Claims 26-27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention or subject matter.

### *Election/Restrictions*

Applicant's election with traverse of 1-12, 14-17, 20-28 and 33-37 in the reply filed on October 27, 2005 is acknowledged.

Claims 13, 18-19, 29-32, and 38-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected claims, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 27, 2005.

Applicant's election of claims 1-12, 14-17, 20-28 and 33-37 and 42 in the reply filed on October 27, 2005. is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

### *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on March 17, 2004 has been considered.

***Claim Objections***

Claim 1 is objected to because Edg-1 shouldt be spelled out upon when first used in a claim. Appropriate correction is required.

Claim 20 is objected to for recitation of non-elected subject matter, all but vasoconstriction (elected) should be deleted.

Claim 27 is objected to because VEGF and cAMP should be spelled out upon when first used in a claim. Appropriate correction is required.

Claims 33-37 are objected to for recitation of non-elected species.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is indefinite with regards to what is the mediated biological activity? The claim also states what the modulator is not; this is not a positive recitation of what "is" the modulator.

Claim 2 is indefinite for the same reason given above (see claim 1 supra).

Claims 3 and 4, these two claims operate in distinctly opposite directions. Unless claim1 and/or 2 indicate specifically that the modulator has two (2) modes of action, then it is not apparent how one (1) modulation has both agonist and antagonist functions. Please note that these two claims only identify the modulator by function, it is

not clear but for "not a phospholipid", what the structure of the modulator would have been.

Claims 5-8 It is not clear which Edg-receptors are or are not included but for Edg 1 in the term " other Edg receptors".

Claims 5-12, 14-17, and 22-23 the phrase "at least about" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "at least about"), thereby rendering the scope of the claim(s) unascertainable because it is not apparent which term is the limiting term. The "at least" in this instance indicates the amount must be ≥200 but the "about" indicates the amount can be less than 200. See MPEP § 2173.05(d).

Claim 21 is also rejected, the phrase "between about" renders the claim indefinite for the reasons paralleling the above discussion of "at least" "about". Next, claim 21 recites "1 fM" but is unclear with regard to the meaning. Is it fem to Molar or is it a typographical error on the basis that if it is fem to molar the range recited is $10^6$ fold difference in binding constants and does not appear to be defined in the specification.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 33-34 and 35-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating vasoconstriction, does not reasonably

provide enablement for preventing all types of vasoconstriction (see Fishman- Acute hypoxia and pulmonary vasoconstriction in humans (2004) and all receptor mediated biological activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The term preventing as determined by examiner means to keep from happening, based upon that, the applicant has not shown any result to convey this.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, 7) the relative skill of those skilled in the art and 8) the quantity of experimentation needed.

1) The nature of the invention: The method of use claims are drawn to preventing vasoconstriction but in view of the report: Acute hypoxia and pulmonary vasoconstriction in humans (2004) indicates (see page 2, left hand col. ¶ 1) that the vasoconstriction is modulated by various mediators and by the autoimmune nervous system and its' intrinsic mechanism is independent of these influences, which does not support applicants' claims in prevention of vasoconstriction, because in other to prevent one most know how and what causes the disease condition.

2) The state of the prior art: The report (see page 2 of Acute hypoxia and pulmonary vasoconstriction in humans (2004) indicates (see page 2, left hand col. ¶ 1) suggests

that preventing allergic rhinitis requires an undue amount of research to successfully attain that goal. "there is currently no completely effective therapy for preventing vasoconstriction. A search for therapeutic agents useful for the prevention of vasoconstriction is ongoing".

3) The predictability or lack thereof in the art: On page 2 of Acute hypoxia and pulmonary vasoconstriction in humans (2004) indicates since the mechanism is unknown, the search for the initiating mechanism continues to present and the approaches vary.

4) The amount of direction or guidance present -The specification only provides examples of inhibition, but did not show how it is related to vasoconstriction and no evidence of prevention in the examples provided, the examples will not enable one skilled in the art to prevent all vasoconstriction, 5) the presence or absence of working examples: The examples shown did not convey prevention of the disease, but only treatment. In addition there is no apparent guidance as to what to expect or how to extrapolate from treating/inhibiting to eradication from the few examples given in the specification.

6) The breadth of the claims: The claims are drawn to methods of preventing.

7) The quantity of experimentation needed would be an undue burden since there is inadequate guidance given to the skilled artisan for the reasons stated above.

8) The relative skill of those skilled in the art. Based on the unpredictable nature of the invention, one skilled in the art would not have envisioned practicing the invention without the exercise of undue experimentation burden.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue and the resultant outcome not predictable.

***Claim Rejections - 35 USC § 102***

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Waeber et al., US 2001/0041688 A1.

Waeber et al. reference disclose a method of modulating (see ¶ 0002) an Edg-1 receptor (see ¶ 0009). The modulator is N,N-dimethyl sphinogosine is not a phospholipids as in the instant claim 1 is recited at (see ¶ 0090). The Waeber et al. reference also discloses a screening method as contacting the cell with the above mentioned compound.

The instant claim 2 is directed to modulating and Edg-1 receptor in a subject by administering a therapeutic effective amount of the Edg-1 receptor wherein the modulator not a phospholipid. The modulator -dimethylsphingosine (not a phospholipid) is recited (see ¶ 0106).

Claim 3, the modulator is an agonist recited (see ¶ 0023) and an atagonist as in current claim 4 (see ¶ 0023).

II. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Au-Young et al., US 5,912,144.

Au-Young et al. disclose a method of modulating an Edg-1 receptor (see col. 1 lines 33+, also col. 4 lines 28+), wherein the modulator Edg-1 is recited as an antisense molecule (see col. 19 lines 44-55) not a phospholipid. The Au-Young et al. also disclose the modulators to be an agonist and an antagonist as in the instant claims 3 and 4 (see abstract).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waeber et al., US 2001/0041688 A1 in view of Au-Young et al., US 5,912,144.

Waeber et al. teach a method of modulating an Edg-1 receptor (see ¶ 0002 also see ¶ 0009), wherein the modulator is N,N-dimethyl sphinogosine is not a phospholipid as in the instant claim 1 is recited at (see ¶ 0090)

The instant claim 2 is directed to modulating and Edg-1 receptor in a subject by administering a therapeutic effective amount of the Edg-1 receptor wherein the modulator not a phospholipid. The modulator -dimethylsphingosine (not a phospholipid) is recited (see ¶ 0106).

The Waeber et al. reference also teaches the modulator of instant claim 3 an agonist (see ¶ 0015) and the instant claim 4 where the modulator is an antagonist (see ¶ 0023).

However, the Waeber et al. reference did not teach the specific fold inhibition selectivity for Edg-1 relative to other Edg receptors as recited in claims 5-12.

Au-Young et al. teach a method of modulating an Edg-1receptor as directed to the current claim 1 (see col. 1 lines 33+, also col. 4 lines 28+), wherein the modulator is recited as an antisense molecule (see col. 19 lines 44-55) not a phospholipid. The Au-Young et al. also teach the modulators to be an agonist and an antagonist as in the instant claims 3 and 4 (see abstract).

Although, the above cited references Waeber et al. and Au-Young et al. did not explicitly teach that the modulators exhibits 5-200 fold inhibitory selectivity, nonetheless. these modulators are of Edg-I antagonist/agonist they obviously carry the properties of

exhibiting the claimed fold inhibitions of the instant claims 5-12, because a chemical composition and its properties are inseparable. Next, the regulation of the inhibitory property is well within the level of the one having ordinary skill in the art, and the artisan would be motivated to determine optimum range to get the maximum effect. Therefore, one of ordinary skill in the art would use the modulators to achieve the same result in the claimed instant subject matter and would have been successful in doing so, because determining the amount of inhibition exhibited is well within the skill of the artisan, which is a normal activity in developing a regimen for its use.

II. Claims 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Au-Young et al., US 5,912,144 in view of Waeber et al., US 2001/0041688 A1.

The teaching of Au-Young et al. is applied here in this rejection as stated above in the preceding rejection. Au-Young also teaches the biological activity is cell proliferation (see col. 16 lines 15-17).

Waeber et al. teach a method of modulating (see ¶ 0002) an Edg-1 receptor (see ¶ 0009), and the modulator N,N-dimethyl sphinogosine is not a phospholipids as recited in the instant claim 1 (see ¶ 0090).

Although, the above cited references Au-Young et al. and Waeber et al. did not explicitly teach that the modulators exhibits 5-200 fold inhibitory selectivity, however, theses modulators are of Edg-I antagonist/agonist they inherently carry the properties of exhibiting the claimed fold inhibitions of the instant claims 5-12, because a chemical composition and its properties are inseparable. Next, the regulation of the inhibitory property is well within the level of the one having ordinary skill in the art, and the artisan

would be motivated to determine optimum range to get the maximum effect. Therefore, one of ordinary skill in the art would use the modulators to achieve the same result in the claimed instant subject matter and would have been successful in doing so, because determining the amount of inhibition exhibited is well within the skill of the artisan, which is a normal activity in developing a regimen for its use.

III. Claims 20-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over in Waeber et al., US 2001/0041688 A1 view of Liao et al., US 2002/0155512 A1.

The teaching of Waeber et al. is applied here in this rejection as stated above in the preceding rejection. Next Waeber et al teach the instant claim 20 the biological activity is vasoconstriction (see ¶ 0002).

Liao et al. teach the modulator of the Edg-1 is 2-amino-2(2-[4-octylphenyl]ethyl)-1,3-propanediol hydrochloride (see ¶ 0204). Absent factual evidence the molecular weight calculated of the compound 2-amino-2(2-[4-octylphenyl]ethyl)-1,3-propanediol hydrochloride is 343.94 Daltons is less than 750 as in claim 25.

With regards to claims 21-23, the Liao et al. reference teaches the binding constant is at least 1 μM (see ¶ 0225) as recited in the current claim 22. Next, the binding constant is at least 10 μM (see ¶ 0225) and absent factual evidence, the binding constant is between 1μM -10 μM (see ¶ 0225) recited in the current claim 21.

It would have been obvious to a person of ordinary skill in the art at the time the claim was made to combine the teachings of Liao et al., and modify the teaching of Waeber et al. and measure the binding constant to result in the claim subject matter.

One having ordinary skill in the art would have been motivated to combine the teachings of the above cited reference because dissociation constant, Kd, indicates the strength of binding between A and B in terms of how easy it is to separate the complex AB (dissociation or 'off rate').

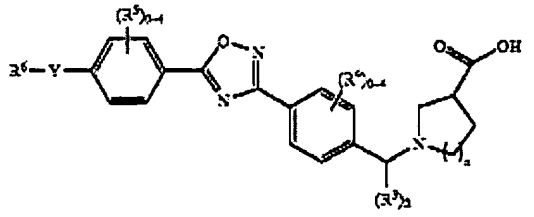
If a high concentration of A and B is required to form AB, this indicates that the strength of binding is low. The Kd would therefore be higher (mM rather than nM) as more of A and B are required to form AB.

It follows that the smaller Kd, the stronger the binding. So $10^{-6}$M (or 1mM) indicates weak binding compared to $10^{-9}$M (or 1nM).

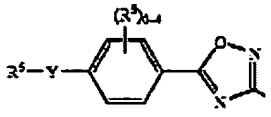
Claim 28, 33-37 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over in Waeber et al., US 2001/0041688 A1 view of Chen et al., US 2005/0245575 A1.

Waeber et al teach the instant claims 33-36 the method of treating vasoconstriction (see ¶ 0002) administering a therapeutic amount (see ¶ 0022).

With regard to claim 28, Chen et al. teach a compound



compounds which are agonist of the Edg-1



receptor that has a core structure as in the instant claim 28 (see ¶ 0010).

The claims differ from the Chen et al. reference by reciting a different species for the treatment of vascular damage (see ¶ 0105).

However, it would have been obvious to one of ordinary skill in the art at the time the claim invention was made to select any of the species of the genus taught by the reference, including those of the claims, because an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties and, thus the same use as the genus as a whole.

Thus, the claimed invention was prima facia obvious to make and use at the time it was made.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SVG
1/21/06

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